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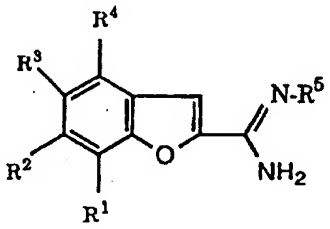
(54) Title: BENZOFURYL DERIVATIVES AND THEIR USE

(57) Abstract

The invention is concerned with the use of compounds of general formula (I) wherein R^1-R^4 signify hydrogen, halogen, lower-alkyl, lower-alkoxy, aryl, benzyloxy, lower-alkoxy-lower-alkyl, lower-alkyl-sulphanyl, lower-alkyl-sulphanyl-lower-alkyl or R^1 and R^2 together signify the group -O-$(CH_2)_2$- or -$(CH_2)_2$-O- and R^5 signifies hydrogen or hydroxy, as well as their pharmaceutically acceptable salts in the control or prevention of illnesses or disorders of the central nervous system such as migraine, schizophrenia, anxiety states, sleep disorders, anorexia, Alzheimer's disease, addictions (alcohol, nicotine, benzodiazepine, cocaine, etc.), as well as disorders which result from damage to the head/brain or to the spinal column/bone marrow and, respectively, for the production of corresponding medicaments.



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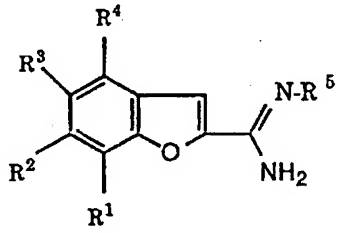
Benzofuryl derivatives and their use

The invention is concerned with benzofuryl derivatives of the general formula



I

wherein

R^1-R^4 signify hydrogen, halogen, lower-alkyl, lower-alkoxy, aryl, benzyloxy, lower-alkoxy-lower-alkyl, lower-alkyl-sulphanyl, lower-alkyl-sulphanyl-lower-alkyl or R^1 and R^2 together signify the group -O-$(CH_2)_2$- or -$(CH_2)_2$-O- and

R^5 signifies hydrogen or hydroxy,

as well as their pharmaceutically acceptable salts.

Some of these compounds are described in EP 0 352 832 for use as broncopulmonary active substances, especially for the treatment of asthma. Furthermore, the unsubstituted amidoxime is known as an antidepressant (Khim. Farm. Zhurnal, vol. 18, No. 11, pp. 1309-1313, 1984). Moreover, analgesic, inflammation-inhibiting and ulcerogenic properties of certain 2-benzofuryl-amidoxime derivatives are described in Eur. J. Med. Chem., No. 6, 1982, pp. 577-581.

It has surprisingly been found that the compounds of formula I have a strong affinity to serotonin receptors, primarily to the 5-HT_{2C} and 5-HT_{2A} receptors, and are accordingly suitable for the treatment of illnesses or disorders of the central nervous system.

Objects of the present invention are the use of compounds of formula I and of pharmaceutically usable salts thereof for the control or prevention of illnesses or disorders of the central nervous system such as migraine, schizophrenia, anxiety states, sleep disorders, anorexia, Alzheimer's disease, addictions (alcohol, nicotine, benzodiazepine, cocaine, etc.), as well as disorders which result from damage to the head/brain or to the spinal column/bone marrow and, respectively, for the production of corresponding medicaments.

Further objects of the present invention are novel compounds from the group of compounds of formula I and their salts, their use as therapeutically active substances, the manufacture of the novel compounds and salts as well as medicaments based thereon and the production of such medicaments.

The term "lower-alkyl" used in the present description denotes straight-chain or branched-chain saturated hydrocarbon residues such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl and the like with up to 7 carbon atoms. The terms "lower-alkoxy" denotes an alkyl residue in the sense of the foregoing definition bonded via an oxygen atom.

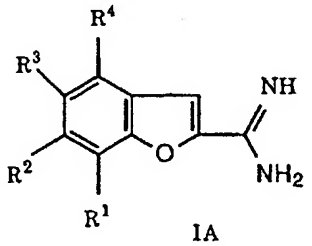
"Halogen" can signify fluorine, chlorine, bromine or iodine.

"Aryl" in the present description signifies phenyl and the like.

The term "pharmaceutically acceptable salts" embraces salts with inorganic and organic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like.

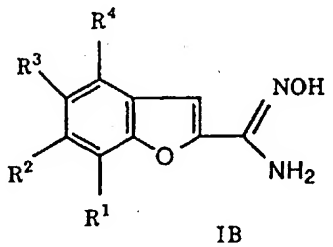
The binding of the compounds of formula I in accordance with the invention to selected serotonin receptors was

determined in vitro by standard methods. It was thereby found that the amidines of the formula



IA

wherein R^1-R^4 have the significance set forth above, show good activities in vitro, while the amidoximes of the formula



IB

wherein R^1-R^4 have the significance set forth above, are only active in vivo. As prodrugs the amidoximes have no affinity to the 5-HT_{2C} receptor. However, they are converted in vivo into the corresponding amidines of formula IA.

Still novel and in the scope of the present invention especially preferred compounds from the group of amidines of formula IA are the following:

5,6-difluorobenzofuran-2-carboxamidine;
4-ethoxybenzofuran-2-carboxamidine;
7-methoxybenzofuran-2-carboxamidine;
7-ethoxybenzofuran-2-carboxamidine;
5-fluorobenzofuran-2-carboxamidine;
6-fluorobenzofuran-2-carboxamidine;
7-ethoxymethylbenzofuran-2-carboxamidine;
6-fluoro-7-propylbenzofuran-2-carboxamidine;
4-fluorobenzofuran-2-carboxamidine;

4,6-difluorbenzofuran-2-carboxamidine;
4-fluoro-6-propyl-benzofuran-2-carboxamidine; and
7-bromo-4-fluoro-benzofuran-2-carboxamidine;

and from the group of amidoximes of formula IB the following:

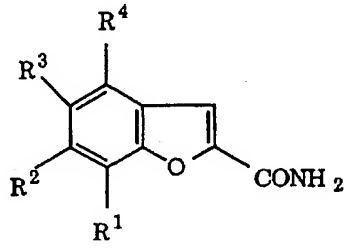
5,6-difluorobenzofuran-2-carboxamidoxime;
7-ethoxybenzofuran-2-carboxamidoxime;
5-fluorobenzofuran-2-carboxamidoxime;
6-fluorobenzofuran-2-carboxamidoxime;
7-ethoxymethylbenzofuran-2-carboxamidoxime; and
4-fluorobenzofuran-2-carboxamidoxime.

Furthermore, the following compounds, which are known per se, are especially suitable for the use referred to above:

benzofuran-2-carboxamidine and
benzofuran-2-carboxamidoxime.

The manufacture of the specifically named novel compounds of formula IA can be effected by

a) reacting a compound of the formula



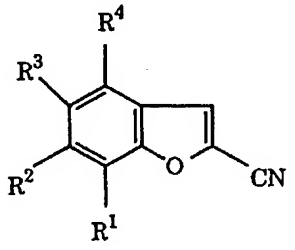
II

wherein

R^1 and R^4	signify hydrogen and	R^2 and R^3 signify fluorine, or
R^1-R^3	signify hydrogen and	R^4 signifies ethoxy, or
R^1	signifies methoxy and	R^2-R^4 signify hydrogen, or
R^1	signifies ethoxy and	R^2-R^4 signify hydrogen, or

R^1, R^2 and R^4 signify hydrogen and R^3 signifies fluorine, or
R^1, R^3 and R^4 signify hydrogen and R^2 signifies fluorine, or
R^1 signifies methyloxyethyl and R^2-R^4 signify hydrogen, or
R^1 signifies n-propyl, R^2 signifies fluorine and R^3 and R^4 signify hydrogen, or
R^1 and R^3 signify hydrogen and R^2 and R^4 signify fluorine, or
R^1 signifies n-propyl, R^4 signifies fluorine and R^2 and R^3 signify hydrogen or
R^1 signifies bromine, R^4 signifies fluorine and R^2 and R^3 signify hydrogen, or
R^1-R^3 signify hydrogen and R^4 signifies fluorine,
with an oxonium salt, preferably with triethyloxonium tetrafluoroborate, and subsequently treating with an ammonium halide, or

b) converting a compound of the formula



III

wherein R^1-R^4 have the significances set forth under a), with H_2S gas into a corresponding thioamide and subsequently reacting this with an ammonium salt in the presence of an alkyl halide, or

c) hydrogenating a compound of formula IB in which R^1-R^4 have the significances set forth under a), and

d) if desired, converting a compound of formula IA into a pharmaceutically acceptable salt.

The manufacture of the specifically named novel compounds of formula IB can be effected by

e) reacting a compound of formula III in which R^1 and R^4 signify hydrogen and R^2 and R^3 signify fluorine, or R^1 signifies ethoxy and R^2-R^4 signify hydrogen, or R^1, R^2 and R^4 signify hydrogen and R^3 signifies fluorine, or R^1, R^3 and R^4 signify hydrogen and R^2 signifies fluorine or R^1 signifies methyloxyethyl and R^2-R^4 signify hydrogen with hydroxylamine, and

f) if desired, converting a compound of formula IB into a pharmaceutically acceptable salt.

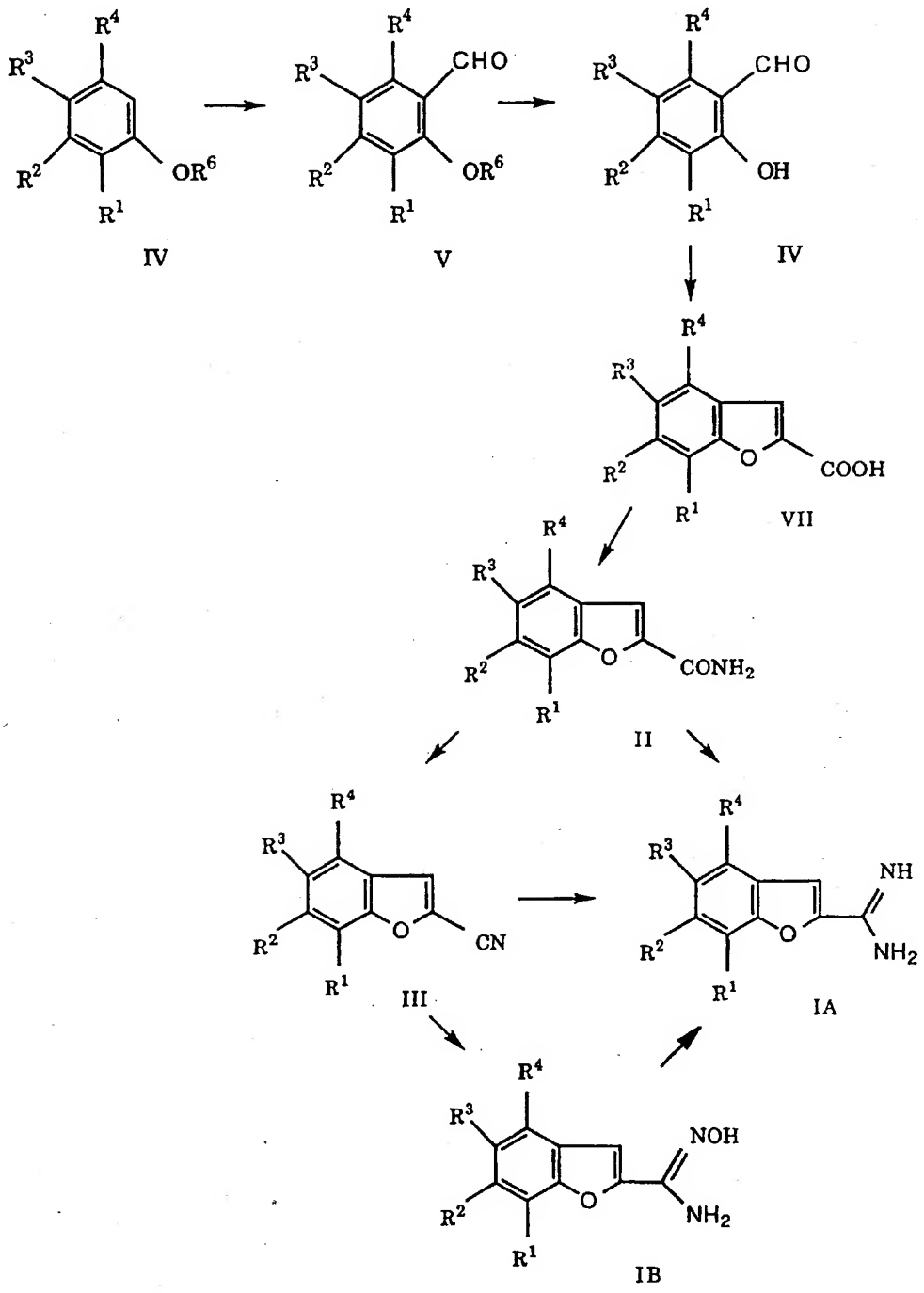
A more detailed description of process variants a), d) and e) set forth above is given in Examples 1-18. The starting materials are known or can be prepared in a generally usual manner illustrated in the Examples hereinafter or in analogy thereto.

In accordance with process variant b) for the manufacture of amidine compounds of formula IA, compounds of formula III are firstly converted into a corresponding thioamide by conducting a H_2S stream through a mixture consisting of a compound of formula III, pyridine and triethylamine. Then, the thioamide is treated with an alkyl halide, for example with methyl iodide, and subsequently reacted with an ammonium salt, preferably with ammonium acetate.

The hydrogenation according to variant c) is effected according to generally usual methods, preferably with Ra-Ni in an ethanol/acetic acid mixture.

The following Scheme illustrates the manufacture of compounds of formula I.

Scheme 1



In this R^1-R^4 have the significance described above and R^6 signifies lower alkyl.

As mentioned earlier, the compounds of formula I have valuable pharmacological properties, since they have a strong binding to serotonin receptors, primarily to 4-HT_{2C} and 5-HT_{2A} receptors, and are accordingly suitable for the treatment or prevention of illnesses or disorders of the central nervous system such as migraine, schizophrenia, anxiety states, sleep disorders, anorexia, Alzheimer's disease, addictions (alcohol, nicotine, benzodiazepine, cocaine, etc.), as well as disorders which result from damage to the head/brain or to the spinal column/bone marrow.

The binding of compounds of formula I in accordance with the invention to selected serotonin inhibitors was determined *in vitro* by standard methods. The preparations were investigated in accordance with the tests given hereinafter:

a) Affinity to the 5-HT_{2C} receptor in accordance with the [3H]-5-HT binding assay according to the method of S.J. Peroutka et al., Brain Research 584, 191-196 (1992).

b) Affinity to the 5-HT_{2A} receptor in accordance with the [3H]-DOB binding assay according to the method of T. Branchek et. al., Molecular Pharmacology 38, 604-609 (1990).

The pK_i values ($pK_i = -\log_{10} K_i$) of the test substances are given. The Ki value is defined by the following formula:

$$K_i = \frac{IC_{50}}{1 + \frac{[L]}{K_D}}$$

with the IC_{50} values being those concentrations of test compounds in nM at which 50% of the receptor-bonded ligands are displaced. [L] is the ligand concentration and the K_D value is the dissocation constant of the ligand.

The thus-determined activity of some compounds in accordance with the invention will be evident from the following Table:

Example No.	R^1	R^2	R^3	R^4	R^5	5-HT_{2C} Method a	5-HT_{2A} Method b
	H	OMe	H	H	H	6.2	5.2
	H	H	OMe	H	H	5.6	<5
	H	H H	H	OMe	H	6.8	5.7
	Me	H	H	H	H	6.4	5.6
	H	Me	H	H	H	6.0	<5
	Cl	H	H	H	H	6.8	5.4
	H	Cl	H	H	H	5.9	5.3
	H	H	Cl	H	H	5.8	5.8
	F	H	H	H	H	6.1	5.3
	H	H	H	H	H	7.1	5.3
	OH	H	H	H	H	6.2	<5
	Oi-Pr	H	H	H	H	6.7	6.0
	OPr	H	H	H	H	6.8	<5
	OBn	H	H	H	H	7.2	6.9
	O-Cyclo-hex	H	H	H	H	6.2	6.8
	Oi-Bu	H	H	H	H	5.7	6.0
	Oi-Pent	H	H	H	H	6.3	6.8
	O-Cyclo-pent	H	H	H	H	6.3	6.6
	Ph	H	H	H	H	6.6	6.8
	Cl	H	Cl	H	H	5.6	6.2
	Br	H	Br	H	H	5.7	6.5
	Br	H	Cl	H	H	5.3	6.5
	i-Prop	H	H	H	H	7.2	6.1
	OMe	H	Br	H	H	6.9	5.6
	OMe	H	Ph	H	H	5.8	6.8
	n-Pr	H	H	H	H	7.1	6.0
	OMe	H	H	Me	H	7.0	5.6
	CH_2-O-Me	H	H	H	H	6.8	5.5
	CH_2-O-iPr	H	H	H	H	6.4	5.7
	CH_2-S-Me	H	H	H	H	6.6	6.0
	Br	H	H	H	H	6.9	5.8
	-O-CH_2-CH_2-		H	H	H	6.4	5.5

	SMe	H	H	H	H	7.1	6.0
1	H	F	F	H	H	6.8	5.7
2	H	H	H	-OEt	H	6.8	<5
3	OMe	H	H	H	H	6.8	<5
4	OEt	H	H	H	H	7.3	<5
5	H	H	F	H	H	6.8	5.7
6	H	F	H	H	H	6.8	5.6
7	$-CH_2-O-Et$	H	H	H	H	7.0	5.7
8	n-Prop	F	H	H	H	7.7	6.8
9	H	H	H	F	H	7.4	5.7
10	H	F	H	F	H	8.1	6.2
11	n-Prop	H	H	F	H	8.1	6.3
12	Br	H	H	F	H	<5	<5
13	H	F	F	H	OH	<5	<5
14	-OEt	H	H	H	OH	5.26	<5
	H	H	H	H	OH	<5	<5
15	H	H	F	H	OH	5.37	<5
16	H	F	H	H	OH	5.36	<5
17	CH_2-OEt	H	H	H	OH	<5	<5
18	H	H	H	F	OH	7.1	5.6

Penile erection (rats)

It has been shown that penile erection is dependent on the stimulation of $5HT_{2C}$ receptors (see Berendsen & Broekkamp, Eur. J. Pharm., 135, 179-184 (1987).

The number of penile erections was determined within 45 minutes following the administration of the test substance to the animals. The ED_{50} is the dosage which causes 50% of these erections.

Example No.	R^1	R^2	R^3	R^4	R^5	ID_{50} (mg/kg) (p.o.)
	H	H	H	H	H	5.0
	H	H	H	H	OH	2.0
1	H	F	F	H	H	6.0
6	H	F	H	H	H	3.0
9	H	H	H	F	H	2.9
16	H	F	H	H	OH	1.6
	$-CH_2O$-i-prop	H	H	H	H	5.1

The compounds of formula I and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active ingredient no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants such as alcohols, polyols, glycerol, vegetable oils and the like can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can also contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a novel compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more novel compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers. The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of intravenous administration a daily dosage of about 1-1000 mg should be appropriate.

The following Examples are intended to illustrate the manufacture of the specific novel compounds in more detail.

Example 1

5,6-Difluorobenzofuran-2-carboxamidine

a) 7.29 ml (66.3 mmol) of titanium tetrachloride were added while stirring to a solution, cooled to 0°, of 5.73 g (39.8 mmol) of 3,4-difluoroanisole in 30 ml of anhydrous dichloromethane. Subsequently, the mixture was treated dropwise over 10 minutes with 3.51 ml (39.6 mmol) of 1,1-dichloromethyl methyl ketone and stirred at room temperature for one hour. The mixture was poured into 100 ml of ice-water, extracted twice with 150 ml of dichloromethane each time and the combined organic phases were washed once with 100 ml of water and once with 100 ml

of saturated sodium chloride solution. After drying over magnesium sulphate concentration was carried out in a vacuum. The crude product obtained was purified by column chromatography on silica gel (hexane/ethyl acetate 4:1). There were obtained 5.8 g (84%) of 4,5-difluoro-2-methoxybenzaldehyde as a white solid with m.p. 74°.

b) A solution of 5.8 g (33.7 mmol) of 4,5-difluoro-2-methoxybenzaldehyde in 400 ml of anhydrous dichloromethane was treated dropwise at -70° while stirring over a period of 10 minutes with 37 ml (37 mmol) of a 1M boron tribromide solution in dichloromethane. Subsequently, the mixture was stirred at room temperature for 16 hours, poured on to 400 ml of ice-water and the phases were separated. The aqueous phase was extracted once with 400 ml of dichloromethane and the combined organic phases were washed once with 200 ml of satrurated sodium chloride solution, dried over magnesium sulphate and concentrated in a vacuum. The crude product obtained was purified by column chromatography on silica gel (hexane/ethyl acetate 4:1). There were obtained 5.05 g (94%) of 4,5-difluoro-2-hydroxybenzaldehyde as a white solid with m.p. 64°.

c) A mixture of 6.5 g (41.1 mmol) of 4,5-difluoro-2-hydroxybenzaldehyde, 10.4 ml (61.7 mmol) of diethyl bromomalonate, 11.3 g (82.2 mmol) of potassium carbonate and 50 ml of ethyl methyl ketone was boiled at reflux for 3 hours while stirring, filtered and concentrated in a vacuum. The brown oil obtained was dissolved in 65 ml of ethanol, treated with 6.5 g of potassium hydroxide pellets and heated at reflux for one hour while stirring. The mixture was concentrated in a vacuum and the residue was treated with 65 ml of water and 65 ml of 3N sulphuric acid and heated at reflux over 30 minutes. Subsequently, the mixture was filtered and the residue was washed with water and triturated in 50 ml of hexane over 30 minutes. The solid was filtered off and dried. There were obtained 4.95 g (60%) of 5,6-difluorobenzofuran-2-carboxylic acid as a light yellow solid with m.p. 270°.

d) A mixture of 4.6 g (23.2 mmol) of 5,6-difluorobenzofuran-2-carboxylic acid and 25 ml of thionyl chloride was heated under reflux for 2.5 hours while stirring. Subsequently, the mixture was concentrated in a vacuum, the residue was dissolved in 20 ml of tetrahydrofuran and the solution was added while stirring at room temperature over a period of 10 minutes to a mixture of 20 ml of ammonium hydroxide solution and 100 ml of tetrahydrofuran. The mixture was stirred at room temperature for a further 30 minutes, poured into 150 ml of saturated sodium chloride solution and extracted twice with 250 ml of ethyl acetate each time. The combined organic phases were washed once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and concentrated in a vacuum. There were obtained 4.38 g (95%) of 5,6-difluorobenzofuran-2-carboxamide as a beige solid with m.p. 217°.

e) A mixture of 1.4 g (7.1 mmol) of 5,6-difluorobenzofuran-2-carboxamide and 1.62 g (8.5 mmol) of triethyloxonium tetrafluoroborate in 40 ml of anhydrous dichloromethane was stirred at room temperature over 64 hours. Subsequently, the mixture was poured into 70 ml of saturated sodium hydrogen carbonate solution, extracted twice with 100 ml of dichloromethane each time and the combined organic phases were washed once with 70 ml of saturated sodium hydrogen carbonate solution, dried over magnesium sulphate and concentrated in a vacuum. The brown solid obtained was dissolved in 30 ml of anhydrous ethanol, treated with 2 g of ammonium chloride and heated under reflux for 22 hours. The mixture was diluted with 90 ml of ethyl acetate and extracted three times with 50 ml of water each time. Subsequently, the combined aqueous phases were made basic with 3N sodium hydroxide solution and the solid was filtered off and washed with water. After drying there was obtained 0.55 g (40%) of 5,6-difluorobenzofuran-2-carboxamidine as a white solid with m.p. 178°.

f) 0.55 g (2.8 mmol) of 5,6-difluorobenzofuran-2-carboxamidine was dissolved in 10 ml of methanol-HCl (2.6N) and

treated at room temperature while stirring with 100 ml of diethyl ether. The mixture was stirred for a further 3 hours and the white crystals were subsequently filtered off. There was obtained 0.61 g (87%) of 5,6-difluorobenzofuran-2-carboxamidine hydrochloride with m.p. >270°.

Example 2

4-Ethoxybenzofuran-2-carboxamidine

a) A mixture of 1 g (5.64 mmol) of 4-hydroxybenzofuran-2-carboxamide, 0.5 ml (6.77 mmol) of ethyl bromide, 1.56 g (11.3 mmol) of potassium carbonate, 6 ml of anhydrous DMF and 50 ml of anhydrous acetone was heated at reflux over 24 hours. Subsequently, the mixture was poured on to 70 ml of ice-water, extracted twice with 100 ml of ethyl acetate each time and the combined organic phases were washed once with 100 ml of saturated sodium chloride solution, dried over magnesium sulphate and concentrated in a vacuum. There were obtained 1.15 g (99%) of 4-ethoxybenzofuran-2-carboxamide as a yellow solid with m.p. 113°.

Further reactions were effected analogously to Example 1e-f. 4-Ethoxybenzofuran-2-carboxamidine hydrochloride was obtained as a white solid with m.p. >220°.

Example 3

7-Methoxybenzofuran-2-carboxamidine

Analogously to Example 1e-f, starting from 7-methoxybenzofuran-2-carboxamide there was obtained 7-methoxybenzofuran-2-carboxamidine hydrochloride as a white solid with m.p. >220°.

Example 4

7-Ethoxybenzofuran-2-carboxamidine

Analogously to Example 1d-f, starting from 7-ethoxybenzofuran-2-carboxylic acid there was obtained 7-ethoxybenzofuran-2-carboxamidine hydrochloride as a white solid with m.p. 190°.

Example 5

5-Fluorobenzofuran-2-carboxamidine

Analogously to Example 1d-f, starting from 5-fluorobenzofuran-2-carboxylic acid there was obtained 5-fluorobenzofuran-2-carboxamidine hydrochloride as a white solid with m.p. >250°.

Example 6

6-Fluorobenzofuran-2-carboxamidine

Analogously to Example 1d-f, starting from 6-fluorobenzofuran-2-carboxylic acid there was obtained 6-fluorobenzofuran-2-carboxamidine hydrochloride as a white solid with m.p. >220°.

Example 7

7-Ethoxymethylbenzofuran-2-carboxamidine

Analogously to Example 1e-f, starting from 7-ethoxymethyl-benzofuran-2-carboxamide there was obtained 7-ethoxymethylbenzofuran-2-carboxamidine hydrochloride as a white solid with m.p. >220°.

The 7-ethoxymethyl-benzofuran-2-carboxamide used was prepared as follows:

a) 4.67 g (16.5 mmol) of ethyl 7-bromomethyl-benzofuran-2-carboxylate were added to a solution of sodium ethanolate in

anhydrous ethanol (freshly prepared from 400 mg (17.4 mmol) of sodium in 40 ml of anhydrous ethanol) and the mixture was heated at reflux for one hour. After cooling to room temperature the mixture was poured into 100 ml of 1N HCl and extracted twice with 150 ml of dichloromethane. After drying over magnesium sulphate concentration was carried out in a vacuum. The crude product obtained was purified by column chromatography on silica gel (dichloromethane). There were obtained 2.8 g (69%) of ethyl 7-ethoxymethyl-benzofuran-2-carboxylate as a pale yellow oil.

b) 40 ml of a 25% aqueous ammonium hydroxide solution were added to a solution of 2.8 g (11.3 mmol) of ethyl 7-ethoxymethyl-benzofuran-2-carboxylate in 20 ml of ethanol and the mixture was stirred at room temperature for three hours. The crystals formed were filtered off and dried in a high vacuum. There were thus obtained 1.66 g (67%) of 7-ethoxymethyl-benzofuran-2-carboxamide as a white solid with m.p. 133-134°.

Example 8

6-Fluoro-7-propylbenzofuran-2-carboxamidine

Analogously to Example 1c-f, starting from 4-fluoro-2-hydroxy-3-propyl-benzaldehyde there was obtained 6-fluoro-7-propylbenzofuran-2-carboxamidine hydrochloride as a white solid with m.p. >220°.

The 4-fluoro-2-hydroxy-3-propyl-benzaldehyde was prepared as follows:

a) 66.7 ml (106.8 mmol) of a 1.6N butyllithium solution in hexane were added at -78° to a solution of 12 g (95.14 mmol) of 3-fluoroanisole in 240 ml of anhydrous tetrahydrofuran and the mixture was stirred for one hour. Subsequently, 21 ml (288 mmol) of propionaldehyde were added dropwise thereto at -78°, the mixture was stirred for one hour and the solution was left to come to room temperature. The mixture was poured into

240 ml of 1N HCl and extracted twice with 250 ml of diethyl ether each time After drying over sodium sulphate concentration was carried out in a vacuum. The crude product obtained was purified by column chromatography on silica gel (dichloromethane/hexane 1:1). There were obtained 15 g (86%) of 1-(2-fluoro-6-methoxy-phenyl)-propan-1-ol as a pale yellow oil.

b) 500 mg of palladium-on-charcoal (10%) were added to a solution of 15 g (81.4 mmol) of 1-(2-fluoro-6-methoxy-phenyl)-propan-1-ol in 200 ml of ethanol and the mixture was hydrogenated at room temperature for 10 hours. The catalyst was filtered off over Dicalite and the filtrate was concentrated in a vacuum. The crude product obtained was purified by column chromatography on silica gel (dichloromethane/hexane 1:2). There were obtained 10.9 g (73%) of 1-fluoro-3-methoxy-2-propyl-benzene as a pale yellow oil.

c) 24 ml (24 mmol) of a 1M boron tribromide solution in dichloromethane were added at -78° to a solution of 3.36 mmol (20 mmol) of 1-fluoro-3-methoxy-2-propyl-benzene in 25 ml of dichloromethane and the mixture was stirred for 10 minutes. After warming to room temperature the mixture was poured cautiously on to 100 ml of ice-water and extracted twice with 250 ml of dichloromethane each time. After drying over sodium sulphate concentration was carried out in a vacuum. The crude product obtained was purified by column chromatography on silica gel (dichloromethane/hexane 4:1). There were obtained 2.9 g (94%) of 3-fluoro-2-propyl-phenol as a pale yellow oil.

d) A solution of 1.4 g (11.7 mmol) of propargyl bromide in 1 ml of dimethylformamide was added dropwise to a suspension of 1.3 g (8.4 mmol) of 3-fluoro-2-propyl-phenol and 1.7 g of potassium carbonate in 4 ml of dimethylformamide and the mixture was subsequently stirred at room temperature for one hour. The mixture was poured on to 30 ml of ice-water and extracted three times with 50 ml of dichloromethane each time. After drying concentration was carried out in a vacuum. The crude product obtained was purified by column chromatography on

silica gel (dichloromethane/hexane 1:1). There were obtained 1.45 g (90%) of 1-fluoro-2-propyl-3-prop-2-ynyloxy-benzene as a pale yellow oil.

e) A suspension of 1.5 g (7.8 mmol) of 1-fluoro-2-propyl-3-prop-2-ynyloxy-benzene and 1.7 g (11.15 mmol) of caesium fluoride in 14 ml of diethylaniline was heated at reflux in a metal bath for 4 hours. After cooling to room temperature 100 ml of diethyl ether were added thereto and insoluble constituents were filtered off. The diethyl ether phase was washed three times with 60 ml of 1N hydrochloric acid, dried over sodium sulphate and concentrated in a vacuum. The crude product obtained was purified by column chromatography on silica gel (dichloromethane/hexane 1:2). There was obtained 0.6 g (40%) of 6-fluoro-2-methyl-7-propyl-benzofuran as a pale yellow oil.

f) Ozone was conducted at -78° into a solution of 4.8 g (25 mmol) of 6-fluoro-2-methyl-7-propyl-benzofuran until the colour became blue. Subsequently, argon was conducted through the solution which was then treated at -78° with 10 ml (136 mmol) of dimethyl sulphide. After warming to room temperature the solution was concentrated in a vacuum and the residue was dissolved in 40 ml of ethanol. After the addition of 20 ml of 3% sodium hydrogen carbonate solution the mixture was stirred at 70° for 30 minutes. Subsequently, the mixture was poured on to 200 ml of ice-water, made acid with 10% HCl and extracted three times with 150 ml of diethyl ether each time. After drying over sodium sulphate concentration was carried out in a vacuum. The crude product obtained was purified by column chromatography on silica gel (dichloromethane). There were obtained 3.3 g (72%) of 4-fluoro-2-hydroxy-3-propyl-benzaldehyde as a pale yellow oil.

Example 9

4-Fluoro-benzofuran-2-carboxamidine

Analogously to Example 1c-f, starting from 6-fluoro-2-hydroxybenzaldehyde there was obtained 4-fluoro-benzofuran-2-carboxamidine hydrochloride as a white solid with m.p. >220°.

Example 10

4,6-Difluoro-benzofuran-2-carboxamidine

Analogously to Example 1c-f, starting from 2,4-difluoro-6-hydroxy-benzaldehyde there was obtained 4,6-difluoro-benzofuran-2-carboxamidine hydrochloride as a white solid with m.p. >250°.

Example 11

4-Fluoro-6-propyl-benzofuran-3-carboxamidine

Analogously to Example 1c-f, starting from 6-fluoro-2-hydroxy-3-propyl-benzaldehyde there was obtained 4-fluoro-6-propyl-benzofuran-3-carboxamidine hydrochloride as a white solid with m.p. 208-210°.

The 6-fluoro-2-hydroxy-3-propyl-benzaldehyde used was prepared as follows:

a) A solution of 42.95 g (0.36 mol) of propargyl bromide in 30 ml of dimethylformamide was added dropwise to a suspension of 50 g (0.26 mol) of 2-bromo-5-fluoro-phenol and 55 g of potassium carbonate in 300 ml of dimethylformamide and the mixture was subsequently stirred at room temperature for two hours. The mixture was poured on to 1500 ml of ice-water and extracted three times with 600 ml of dichloromethane each time. After drying over sodium sulphate concentration was carried out in a vacuum. The crude product obtained was purified by column

chromatography on silica gel (dichloromethane/hexane 1:1). 58 g (97%) of 1-bromo-4-fluoro-2-prop-2-ynyloxy-benzene were obtained as a pale yellow oil.

b) A suspension of 57 g (250 mmol) of 1-bromo-4-fluoro-2-prop-2-ynyloxy-benzene and 53 g (350 mmol) of caesium fluoride in 400 ml of diethylaniline was heated at reflux in a metal bath for 4 hours. After cooling to room temperature 1500 ml of diethyl ether were added thereto and the insoluble constituents were filtered off. The diethyl ether phase was washed three times with 600 ml of 1N hydrochloric acid, dried over sodium sulphate and concentrated in a vacuum. The crude product obtained was purified by column chromatography on silica gel (hexane). 51.4 g (89%) of 7-bromo-4-fluoro-2-methyl-benzofuran were obtained as a pale yellow oil.

c) A solution of 5.75 g (25.1 mmol) of 7-bromo-4-fluoro-2-methylbenzofuran in 90 ml of tetrahydrofuran was added dropwise to a suspension of 0.625 g (27.5 mmol) of Mg in 100 ml of boiling tetrahydrofuran and the mixture was stirred at reflux for 2.5 hours. Subsequently, it was cooled to 10°C, 2.75 ml (37.5 mmol) of propionaldehyde were added dropwise thereto and the mixture was stirred for 30 minutes. The mixture was poured into 200 ml of 1N hydrochloric acid and extracted three times with 150 ml of dichloromethane. After drying over sodium sulphate concentration was carried out in a vacuum. The crude product obtained was purified by column chromatography on silica gel (dichloromethane/hexane 4:1). 3.6 g (55%) of 1-(4-fluoro-2-methyl-benzofuran-7-yl)-propan-1-ol were obtained as a pale yellow oil.

d) A suspension of 4.0 g (19.2 mmol) of 1-(4-fluoro-2-methyl-benzofuran-7-yl)-propan-1-ol and 0.7 g of Pd/C in 60 ml of ethanol was hydrogenated for 2 hours. The catalyst was filtered off, the ethanol was evaporated in a vacuum and the crude product obtained was purified by column chromatography on silica gel (dichloromethane/hexane 4:1). There were obtained 2.6 g (72%) of a 4:1 mixture of 4-fluoro-2-methyl-7-propyl-

benzofuran and 4-fluoro-2-methyl-7-propyl-2,3-dihydro-benzofuran, which was used as such in the next reaction.

e) Ozone was conducted at -78°C into a solution of 6.6 g (34 mmol) of a 4:1 mixture of 4-fluoro-2-methyl-7-propyl-benzofuran and 4-fluoro-2-methyl-7-propyl-2,3-dihydro-benzofuran until the colour became blue. Subsequently, argon was conducted through the solution which was then treated at -78°C with 13 ml of dimethyl sulphide. After warming to room temperature the solution was concentrated in a vacuum and the residue was dissolved in 50 ml of ethanol. After the addition of 50 ml of 3% sodium hydrogen carbonate solution the mixture was stirred at 70°C for 30 minutes. Subsequently, the mixture was poured on to 200 ml of ice-water, made acid with 10% HCl and extracted three times with 150 ml of diethyl ether each time. After drying over sodium sulphate concentration was carried out in a vacuum. The crude product obtained was purified by column chromatography on silica gel (dichloromethane/hexane 2:3). There were obtained 5.0 g (100%) of 6-fluoro-2-hydroxy-3-propyl-benzaldehyde as a pale yellow oil, which was used immediately in the next reaction.

Example 12

7-Bromo-4-fluorobenzofuran-2-carboxamidine

Analogously to Example 1c-f, starting from 3-bromo-6-fluoro-2-hydroxybenzaldehyde there was obtained 7-bromo-4-fluoro-benzofuran-2-carboxamidine hydrochloride as a white solid with m.p. >230°.

The 3-bromo-6-fluoro-2-hydroxy-benzaldehyde used was prepared as follows:

Ozone was conducted into a solution of 8.0 g (35 mmol) of 7-bromo-4-fluoro-2-methylbenzofuran at -78°C until the colour became blue. Subsequently, argon was conducted through the solution which was then treated at -78°C with 13 ml of dimethyl

sulphide. After warming to room temperature the solution was concentrated in a vacuum and the residue was dissolved in 50 ml of ethanol. After the addition of 50 ml of 3% sodium hydrogen carbonate solution the mixture was stirred at 70° for 30 minutes. Subsequently, the mixture was poured on to 200 ml of ice-water, made acid with 10% HCl and extracted three times with 150 ml of diethyl ether. After drying over sodium sulphate concentration was carried out in a vacuum. The crude product obtained was purified by column chromatography on silica gel (dichloromethane/hexane 4:1). There were obtained 7.5 g (98%) of 3-bromo-6-fluoro-2-hydroxy-benzaldehyde as a pale yellow oil, which was used immediately in the next reaction.

Example 13

5,6-Difluorobenzofuran-2-carboxamidoxime

a) 1.5 g (7.61 mmol) of 5,6-difluorobenzofuran-2-carboxamide were treated with 8 ml of phosphorus oxychloride and heated under reflux over a period of 5 minutes while stirring. Subsequently, the clear solution was added dropwise while stirring to a mixture of 36 ml of ammonium hydroxide solution and 64 g of ice, with the temperature not exceeding 20°. The mixture was stirred for a further 30 minutes and the beige crystals were subsequently filtered off. There were obtained 1.2 g (88%) of 5,6-difluorobenzofuran-2-carbonitrile as a beige solid with m.p. 103°.

b) A mixture of 1.2 g (6.7 mmol) of 5,6-difluorobenzofuran-2-carbonitrile, 0.93 g (13.4 mmol) of hydroxylamine hydrochloride, 2.78 g (20.1 mmol) of potassium carbonate and 50 ml of anhydrous ethanol was heated under reflux over 16 hours while stirring. Subsequently, the solid was filtered off and the filtrate was concentrated in a vacuum. The crude product obtained was purified by column chromatography on silica gel (ethyl acetate/hexane 3:2). There was obtained 0.88 g (61%) of 5,6-difluorobenzofuran-2-carboxamidoxime as a light yellow solid with m.p. 184°.

c) 0.88 g (4.15 mmol) of 5,6-difluorobenzofuran-2-carboxamidoxime was dissolved in 5 ml of methanol-HCl (2.6N) and treated at room temperature while stirring with 100 ml of diethyl ether. The mixture was stirred for a further 4 hours and the white crystals were subsequently filtered off. There were obtained 1.01 g (98%) of 5,6-difluorobenzofuran-2-carboxamidoxime hydrochloride with m.p. 193°.

Example 14

7-Ethoxybenzofuran-2-carboxamidoxime

Analogously to Example 13a-c, starting from 7-ethoxybenzofuran-2-carboxamide there was obtained 7-ethoxybenzofuran-2-carboxamidoxime hydrochloride as a light yellow solid with m.p. 171°.

Example 15

5-Fluorobenzofuran-2-carboxamidoxime

Analogously to Example 13a-c, starting from 5-fluorobenzofuran-2-carboxamide there was obtained 5-fluorobenzofuran-2-carboxamidoxime hydrochloride as a white solid with m.p. 203-204°.

Example 16

6-Fluorobenzofuran-2-carboxamidoxime

Analogously to Example 13a-c, starting from 6-fluorobenzofuran-2-carboxamide there was obtained 6-fluorobenzofuran-2-carboxamidoxime hydrochloride as a white solid with m.p. 224-225°.

Example 17

7-Ethoxymethylbenzofuran-2-carboxamidoxime

Analogously to Example 13a-c, starting from 7-ethoxymethylbenzofuran-2-carboxamide there was obtained 7-ethoxymethylbenzofuran-2-carboxamidoxime hydrochloride as a white solid with m.p. 200-202°.

Example 18

4-Fluorobenzofuran-2-carboxamidoxime

Analogously to 13a-c, starting from 4-fluorobenzofuran-2-carboxamide there was obtained 4-fluorobenzofuran-2-carboxamidoxime hydrochloride as a white solid with m.p. 186-188°.

Example A

Tablets of the following composition are produced in the usual manner:

	mg/Tablet
Active ingredient	100
Powd. lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Tablet weight	250

Example B

Tablets of the following composition are produced in the usual manner:

mg/Tablet

Active ingredient	200
Powd. lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

Example C

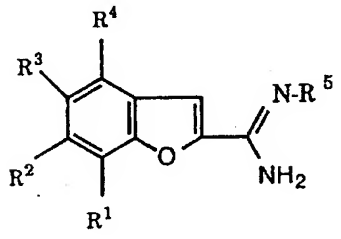
Capsules of the following composition are produced:

	mg/Capsule
Active ingredient	50
Cryst. lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	150

The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The finished mixture is filled into hard gelatine capsules of suitable size.

Claims

1. The use of compounds of the general formula



I

wherein

R^1-R^4 signify hydrogen, halogen, lower-alkyl, lower-alkoxy, aryl, benzyloxy, lower-alkoxy-lower-alkyl, lower-alkyl-sulphanyl, lower-alkyl-sulphanyl-lower-alkyl or R^1 and R^2 together signify the group -O-$(CH_2)_2$- or -$(CH_2)_2$-O- and

R^5 signifies hydrogen or hydroxy,

as well as their pharmaceutically acceptable salts in the control or prevention of illnesses or disorders of the central nervous system such as migraine, schizophrenia, anxiety states, sleep disorders, anorexia, Alzheimer's disease, addictions (alcohol, nicotine, benzodiazepine, cocaine, etc.), as well as disorders which result from damage to the head/brain or to the spinal column/bone marrow and, respectively, for the production of corresponding medicaments.

2. The use of

5,6-difluorobenzofuran-2-carboxamidine,
4-ethoxybenzofuran-2-carboxamidine,
benzofuran-2-carboxamidine,
7-methoxybenzofuran-2-carboxamidine,
7-ethoxybenzofuran-2-carboxamidine,
5-fluorobenzofuran-2-carboxamidine,
6-fluorobenzofuran-2-carboxamidine,
7-ethoxymethylbenzofuran-2-carboxamidine,

6-fluoro-7-propylbenzofuran-2-carboxamidine,
4-fluorobenzofuran-2-carboxamidine,
4,6-difluorobenzofuran-2-carboxamidine,
4-fluoro-6-propyl-benzofuran-2-carboxamidine and
7-bromo-4-fluoro-benzofuran-2-carboxamidine,

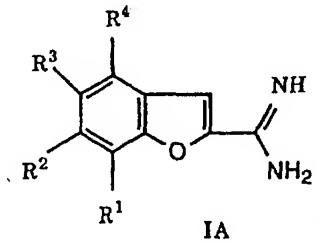
in accordance with claim 1.

3. The use of

5,6-difluorobenzofuran-2-carboxamidoxime,
7-ethoxybenzofuran-2-carboxamidoxime,
benzofuran-2-carboxamidoxime,
5-fluorobenzofuran-2-carboxamidoxime,
6-fluorobenzofuran-2-carboxamidoxime,
7-ethoxymethylbenzofuran-2-carboxamidoxime and
4-fluorobenzofuran-2-carboxamidoxime

in accordance with claim 1.

4. Compounds of the general formula



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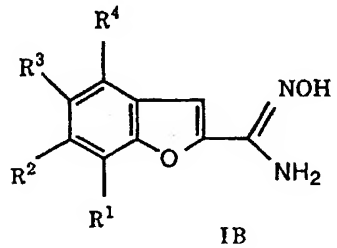
wherein

R^1 and R^4 signify hydrogen and R^2 and R^3 signify fluorine, or
R^1-R^3 signify hydrogen and R^4 signifies ethoxy, or
R^1 signifies methoxy and R^2-R^4 signify hydrogen, or
R^1 signifies ethoxy and R^2-R^4 signify hydrogen, or
R^1, R^2 and R^4 signify hydrogen and R^3 signifies fluorine, or
R^1, R^3 and R^4 signify hydrogen and R^2 signifies fluorine, or
R^1 signifies methyloxyethyl and R^2-R^4 signify hydrogen, or
R^1 signifies n-propyl, R^2 signifies fluorine and R^3 and

R^4 signify hydrogen or
R^1-R^3 signify hydrogen and R^4 signifies fluorine.

5. Compounds of the general formula



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wherein
R^1 and R^4 signify hydrogen and R^2 and R^3 signify fluorine, or
R^1 signifies ethoxy and R^2-R^4 signify hydrogen, or
R^1, R^2 and R^4 signify hydrogen and R^3 signifies fluorine, or
R^1, R^3 and R^4 signify hydrogen and R^2 signifies fluorine, or
R^1 signifies methyloxyethyl and R^2-R^4 signify hydrogen.

6. 5,6-Difluorobenzofuran-2-carboxamidine,
4-ethoxybenzofuran-2-carboxamidine,
7-methoxybenzofuran-2-carboxamidine,
7-ethoxybenzofuran-2-carboxamidine,
5-fluorobenzofuran-2-carboxamidine,
6-fluorobenzofuran-2-carboxamidine,
7-ethoxymethylbenzofuran-2-carboxamidine,
6-fluoro-7-propylbenzofuran-2-carboxamidine,
4-fluorobenzofuran-2-carboxamidine,
4,6-difluorobenzofuran-2-carboxamidine,
4-fluoro-6-propyl-benzofuran-2-carboxamidine,
7-bromo-4-fluoro-benzofuran-2-carboxamidine,

in accordance with claim 4.

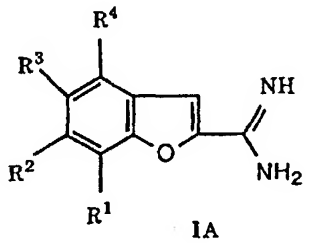
7. 5,6-Difluorobenzofuran-2-carboxamidoxime,
7-ethoxybenzofuran-2-carboxamidoxime,
5-fluorobenzofuran-2-carboxamidoxime,

6-fluorobenzofuran-2-carboxamidoxime,
7-ethoxymethylbenzofuran-2-carboxamidoxime,
4-fluorobenzofuran-2-carboxamidoxime,

in accordance with claim 5.

8. A medicament, especially for the control or prevention of illnesses or disorders of the central nervous system such as migraine, schizophrenia, anxiety states, sleep disorders, anorexia, Alzheimer's disease, addictions (alcohol, nicotine, benzodiazepine, cocaine, etc.), as well as disorders which result from damage to the head/brain or to the spinal column/bone marrow, containing one or more compounds according to any one of claims 4-7 and a therapeutically inert excipient.

9. A process for the manufacture of compounds of the formula



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wherein

R^1 and R^4	signify hydrogen and R^2 and R^3 signify fluorine, or
R^1-R^3	signify hydrogen and R^4 signifies ethoxy, or
R^1	signifies methoxy and R^2-R^4 signify hydrogen, or
R^1	signifies ethoxy and R^2-R^4 signify hydrogen, or
R^1, R^2 and R^4	signify hydrogen and R^3 signifies fluorine, or
R^1, R^3 and R^4	signify hydrogen and R^2 signifies fluorine, or
R^1	signifies methyloxyethyl and R^2-R^4 signify hydrogen, or
R^1	signifies n-propyl, R^2 signifies fluorine and R^3 and R^4 signify hydrogen, or
R^1 and R^3	signify hydrogen and R^2 and R^4 signify fluorine, or
R^1	signifies n-propyl, R^4 signifies fluorine and R^2 and R^3

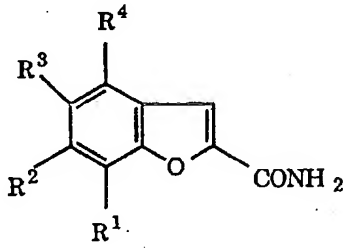
signify hydrogen or

R^1 signifies bromine, R^4 signifies fluorine and R^2 and R^3 signify hydrogen, or

R^1-R^3 signify hydrogen and R^4 signifies fluorine,

which process comprises

a) reacting a compound of the formula



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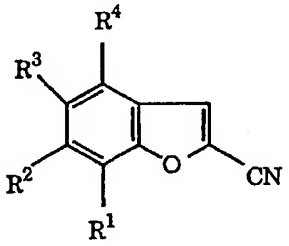
wherein R^1-R^4 have the significance set forth earlier in this claim,

with an oxonium salt, preferably with triethyloxonium tetrafluoroborate, and subsequently treating with an ammonium halide, or

b) converting a compound of the formula



III

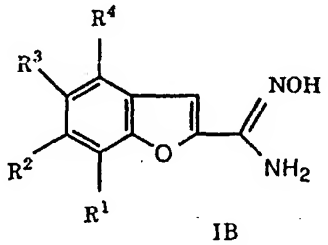
wherein R^1-R^4 have the significance set forth earlier in this claim,

with H_2S gas into a corresponding thioamide and subsequently reacting this with an ammonium salt in the presence of an alkyl halide, or

c) hydrogenating a compound of formula IB in which R^1-R^4 have the significance set forth earlier in this claim, and

d) if desired, converting a compound of formula IA into a pharmaceutically acceptable salt.

10. A process for the manufacture of compounds of the formula



IB

wherein

R^1 and R^4 signify hydrogen and R^2 and R^3 signify fluorine, or

R^1 signifies ethoxy and R^2-R^4 signify hydrogen, or

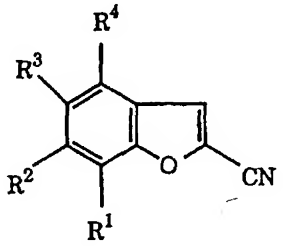
R^1, R^2 and R^4 signify hydrogen and R^3 signifies fluorine, or

R^1, R^3 and R^4 signify hydrogen and R^2 signifies fluorine, or

R^1 signifies methyloxyethyl and R^2-R^4 signify hydrogen,

which process comprises

e) reacting a compound of the formula



III

wherein R^1, R^2, R^3 and R^4 have the significance set forth earlier in this claim,

with hydroxylamine and

f) if desired, converting a compound of general formula IB into a pharmaceutically acceptable salt.

11. Compounds according to any one of claims 4-7, whenmanufactured by a process according to claim 9 or 10 or a process equivalent thereto.

12. Compound according to any one of claims 4-7 for use as therapeutically active substances, especially for the control or prevention of illnesses or disorders of the central nervous system.

13. The use of compounds according to any one of claims 4-7 as therapeutically active substances.

14. The use of compounds according to any one of claims 4-7 in the control or prevention of illnesses or disorders of the central nervous system such as migraine, schizophrenia, anxiety states, sleep disorders, anorexia, Alzheimer's disease, addictions (alcohol, nicotine, benzodiazepine, cocaine, etc.), as well as disorders which result from damage to the head/brain or to the spinal column/bone marrow and, respectively, for the production of corresponding medicaments.

15. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

Inte...uonal Application No
PCT/EP 97/02092

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D307/85 C07D307/86 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 352 832 A (AKZO N.V.) 31 January 1990 cited in the application see the whole document ---	1-14
A	EUROPEAN JOURNAL OF MEDICINAL CHEMISTRYCHIMICA THERAPEUTICA., vol. 17, no. 6, 1982, PARIS FR, pages 577-580, XP002036825 J.P. RIFFAUD ET AL.: "Sur les propriétés analgésiques et antiinflammatoires des benzofuryl-2 amidoximes" cited in the application see the whole document --- -/--	1-14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 August 1997	13.08.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte.. .ional Application No
PCT/EP 97/02092

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 92, no. 9, 3 March 1980 Columbus, Ohio, US; abstract no. 76203, SHRIDHAR D.R. ET AL.: "Benzofuran derivatives" XP002036826 see abstract & INDIAN J. CHEM., SECT. B, vol. 18B, no. 3, 1979, INDIA, pages 254-256, -----	1-14

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

ernational application No.

PCT/EP 97/02092

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 1-3, 14
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 15
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

See Rule 6.2 (a)

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte.. ..ional Application No
PCT/EP 97/02092

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 352832 A	31-01-90	AU 619567 B	30-01-92
		AU 3783789 A	11-01-90
		ES 2051986 T	01-07-94
		IE 60969 B	07-09-94
		JP 2085241 A	26-03-90
		PT 91057 B	30-12-94
		US 5026724 A	25-06-91